B2 28. (Twice Amended) A therapeutic composition for the treatment of staphylococcal infection in humans, comprising at least one recombinantly produced lysostaphin analogue having the biological activity of proteolytic attack against glycine-containing bridges in the cell wall peptidoglycan of staphylococci and a pharmaceutically acceptable carrier, wherein the composition is suitable for systemic administration.

B3 35. (Amended) The composition of claim 28 further comprising at least one rifamycin or glycopeptide or combination thereof.

REMARKS

Status of the Application

Claims 4, 5, 28, 29 and 32-55 are pending in the present application. The Examiner rejects all of the pending claims under 35 U.S.C. § 103(a). By this Amendment, Applicants have canceled Claims 29 and 40 and have amended Claims 4, 5, 28 and 32. The amendments to Claims 4, 5, and 28 are to clarify that the method and composition of the present invention are for the treatment of humans and that administration is systemically. Support for the amendments may be found in the Specification at, for example, page 1, lines 18-20 and page 6, lines 28-32. The amendment to Claim 35 is to change the dependency from Claim 28 and canceled Claim 29 to only Claim 28. In view of the foregoing amendments and the following remarks, Applicants respectfully request withdrawal of the rejections set forth in the outstanding Office Action.

Rejection under 35 U.S.C. § 103(a)

Claims 4, 5, 28 and 29

The Examiner rejects Claims 4, 5, 28 and 29 under 35 U.S.C. § 103(a) as obvious over Zygmunt or Stark or Goldberg in view of Oldham. Because Claim 29 has been canceled, its

rejection is moot. Applicants respectfully traverse the rejection of Claims 4, 5 and 28.

Claims 4, 5 and 28 are drawn to methods and compositions for treating staphylococcal infections in humans comprising systemically administering an effective amount of at least one recombinantly produced lysostaphin analogue. None of the primary references (e.g., Zygmunt, Stark and Goldberg) disclose systemic treatment of humans using recombinant lysostaphin. Indeed, Zygmunt and Goldberg relate to treating staphylococcal infections in animals such as dogs and mice using lysostaphin. While Stark discloses treatment in a human, the study involved a single human and is more speculative of treatment in man than conclusive, as indicated by the article's title. Moreover, the patient died three days after administration of the lysostaphin, making long-term study impossible.

The Examiner acknowledges that the primary references do not teach recombinant lysostaphin or use thereof. See Final Office Action dated June 4, 2001, page 4. The Examiner, therefore, resorts to Oldham to demonstrate that lysostaphin can be produced recombinantly and that such product has activity similar to that of natural lysostaphin. See Final Office Action dated June 4, 2001, page 4.

Reference to Oldham, however, is inappropriate. First, Oldham is limited to the treatment of a specific staphylococcal infection not found in humans, namely bovine mastitis. As discussed by Michael Climo, M.D. in the accompanying Declaration under 37 C.F.R. § 1.132, treatment of bovine mastitis is not predictive of treatment of staphylococcal infections in humans. See Declaration under 37 C.F.R. § 1.132, page 3, ¶ 11. Second, Oldham is further confined to localized treatment of mastitis, i.e., infusion of bovine mammary glands, with recombinant lysostaphin and fails to teach systemic administration of recombinant lysostaphin. Indeed, use of recombinant lysostaphin in a non-systemic model is certainly not predictive of systemic treatment

in humans. See Declaration under 37 C.F.R. § 1.132, page 4, ¶ 12. Third, Oldham discloses that recombinant lysostaphin is highly immunogenic in systemic administration. See pages 4181-4182. This disclosure alone is sufficient to teach away from the instant invention. See Declaration under 37 C.F.R. § 1.132, page 4, ¶ 13. In fact, the very method identified by Oldham as posing problems with immunogenicity, i.e., parenteral administration, is precisely the method taught by the primary references cited by the Examiner. See, e.g., Zygmunt, page 237. Whatever the primary references may or may not teach about naturally-occurring lysostaphin, it is clear, therefore, that the teaching in the art is that recombinant lysostaphin is immunogenic when administered systemically. Fourth, the data suggests that even if recombinant lysostaphin is administered locally, curing of the staphylococcal infection does not ensue in a high percentage of the cases. See, e.g., Oldham, page 4180, Table 3. Fifth, Oldham fails to teach that low doses, i.e., less than 50 mg/kg, of recombinant lysostaphin cure the staphylococcal infection. Indeed, Oldham injected into the infected teat canal single doses of 0, 1, 10, 100 or 500 mg of recombinant lysostaphin. The only doses that elicited any cures were the 100 mg and 500 mg doses. See Oldham, page 4178, second column. According to Oldham, "[t]he in vivo dose titration suggested that the minimal effective therapeutic dose was 100 mg of [recombinant lysostaphin]." See Oldham, page 4180, second column.

Claims 32 and 35

The Examiner rejects Claims 32 and 35 under 35 U.S.C. §103(a) as being unpatentable over Zygmunt or Stark or Goldberg in view of Oldham as applied to Claims 4, 5, 28 and 29 and further in view of Dixon. Applicants respectfully traverse.

According to the Examiner, Dixon teaches "that it is preferable to use lysostaphin in combination with other antimicrobials because a single dose usage of lysostaphin reduces dangers of hypersensitivity reaction." See Office Action dated June 4, 2001, page 7. Applicants assert

that the Examiner's rejection involves an inappropriate reading of the cited disclosure and, therefore, should be withdrawn.

Applicants initially note that, other than Zygmunt and Dixon, the cited references are silent with respect to combinatorial therapy and, in fact, focus on the administration of lysostaphin alone and warn about the complications associated with such. As the Examiner acknowledges, Zygmunt teaches sequential administration of antimicrobials, i.e., lysostaphin followed by another antibiotic. The specific strategy behind the Zygmunt teaching of initial administration of lysostaphin followed by an antibiotic is the idea that lysostaphin will reduce high bacterial titers in emergency situations, thereby enhancing efficacy of any conventional antibiotics subsequently administered. Such teaching not only renders the instant invention not obvious but also teaches away from the instant invention.

Like Zygmunt, Dixon teaches sequential administration of lysostaphin followed by another antibiotic. In particular, Dixon discloses treating staphylococci within established renal abscesses in mice with a single dose of lysostaphin followed by four daily doses of methicillin. See Dixon, page 68. Dixon, however, does not teach or suggest simultaneous administration of lysostaphin and another antibiotic.

The instant claims, on the other hand, require that lysostaphin be combined and administered together with another antibiotic. This is contrary to the teachings of Zygmunt and Dixon. Both Zygmunt and Dixon teach sequential administration, administration first of a single dose of lysostaphin in the hope of initially blunting the infection while avoiding adverse reactions and resistance (i.e., hypersensitivity) and then of another antibiotic. The teachings of Zygmunt and Dixon are clearly not that of the present invention, nor are they suggestive thereof.

In order to establish a *prima facie* case of obviousness, "the prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP 706.02(j).

When combined, it is obvious that Zygmunt or Stark or Goldberg in view of Oldham and further in view of Dixon do not teach the simultaneous administration of rifamycin or glycopeptides with recombinant lysostaphin.

Claims 33, 34 and 36-55

The Examiner also rejects Claims 33, 34 and 36-55 under 35 U.S.C. §103(a) as being unpatentable over Zygmunt and Stark and Goldberg and Oldham. Applicants respectfully traverse.

The instant claims are drawn to particular dosage amounts. The Examiner correctly asserts that the primary references teach different dosages of lysostaphin. What the Examiner does not appear to appreciate, however, is that the combination of the references does not teach or suggest systemic treatment of staphylococcal infections in humans using the particular dosage amounts of recombinantly produced lysostaphin, either alone or in combination with another antibiotic, as taught by Applicants. The only human study (i.e., Stark) used a single 500 mg dose of lysostaphin. While Zygmunt and Goldberg teach the use of lysostaphin alone in dosages ranging from 0.5 to 50 mg/kg, the lysostaphin is not recombinantly produced lysostaphin. The only teaching of recombinant lysostaphin specifically notes that the data suggests that 100 mg of recombinant lysostaphin is the "minimal effective therapeutic dose." See Oldham, page 4180.

Conclusion

For the reasons discussed above and in the accompanying declaration, Applicants respectfully submit that the present invention is not obviousness in view of the references cited by the Examiner. Applicants, therefore, request withdrawal of the rejections. As the claims are otherwise in compliance with the requirements of Title 35, they are in condition for allowance, and notice of the same is respectfully requested. If any points remain in issue that the Examiner

feels may be best resolved through a personal or telephonic interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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MARKED-UP COPY OF AMENDED CLAIMS

4. (Twice Amended) A method of treating a staphylococcal infection of at least one organ or tissue selected from the group consisting of heart valve, blood, kidney, lung, bone and meninges, comprising systemically administering to a [mammal] human suffering from at least one of said infections an effective amount of at least one recombinantly produced lysostaphin analogue.

5. (Twice Amended) A method of treating a staphylococcal infection associated with a catheter or a prosthetic device, comprising systemically administering to a [mammal] human suffering from such an infection an effective amount of at least one recombinantly produced lysostaphin analogue.

28. (Twice Amended) A therapeutic composition for the treatment of staphylococcal infection in humans, comprising at least one recombinantly produced lysostaphin analogue having the biological activity of proteolytic attack against glycine-containing bridges in the cell wall peptiglycan of staphylococci and a pharmaceutically acceptable carrier, wherein the composition is suitable for systemic administration.

35. (Amended) The composition of claim 28 [or 29] further comprising at least one rifamycin or glycopeptide or combination thereof.